ALPHARMA,
U S Pharmaceuticals Division

8562 '99 AUG 27 A9:24

August 23, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir:

We wish to thank the agency for this opportunity to offer our comments on the draft Guidance for Industry; Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing, and Controls Documentation. We hope that our comments will help improve this document and make it more useful to all concerned.

To help understand what we intend with the various comments we have used the following rule, when wording is suggested, new words are *italicized* and deletions are ~~crossed out~~. Each specific comment is referenced to the Initial Line Number.

General comments

1. Standard ICH nomenclature should be employed where practical. An example would be to use Active Pharmaceutical Ingredient (API) and not drug substance.

2. The need for a separate study to demonstrate that the packaging and the formulation are compatible is not included in the guidance. Such a study is a key part of the development of a suitable nasal spray. Such a study involves the exposure of the various components making up the pump system to the formulation or formulation vehicle to determine if any materials are extracted from the packaging and if any of the components of the formulation are lost to the packaging. Such a study can be conducted using stress conditions, such 55°C for a month to keep it to a reasonable time frame. GC and. HPLC can then be used to examine the samples. A protocol for such a study will be provided if desired.

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3. **In section III.G. the statement is made that "The use of some type of dose counting mechanism for these products is encouraged." As a generic manufacturer there is no mechanism for us to add this type of mechanism to the product to the patients' benefit. We recommend that the Agency consider mechanisms to permit product upgrades by generic manufacturer particularly when patient safety is concerned.**

4. **There are repeated references in the body of the Guidance to the "analytical sampling plan." The sampling plans used have been defined as a GMP issue, which is addressed by the Compliance Division and therefore should not be a routine part of submissions.**

5. **Wherever possible this guidance should refer to other specific guidances and not repeat sections from them. This will greatly simplify revision and make use of the guidance easier for all concerned.**

Specific Comments

Section III.C.I

Line 140 **Since the previous line states "...per unit volume or weight..." this line should be changed to either "...target container fill weight** *or* **volume should also..." or "...target container net contents** ~~fill weight~~ **should also..."**

Line 144 We assume that the reference to "excesses" in this line was meant to apply to an excess of the active pharmaceutical ingredient, but this is not clear. If the intent is to also apply this statement to the fill volume, then an excess added to assure compliance with a deliverable volume for an inhalation solution must also be permitted. The following change in wording is suggested. The second suggested sentence is required depending on the answer to the above discussion.

"For these products, an *excess* **of** *the active pharmaceutical ingredient* **should only be included for justified reproducible manufacturing losses.** *An excess fill should on/y be to* **assure** *the deliverable volume of* **an** *inhalation product."*

Line 166 When the word "density" is stated in this context we assume that the test being referred to is bulk density or tapped bulk density. While standardized test methods have not yet been established in the USP, this test may be of value when applied to an API or excipient intended for use

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in tableting. However, it offers no useful knowledge when applied to an API intended for use in a solution or suspension. Particle size is an adequate control for these dosage forms, so we recommend deleting density.

Line 175 The requirement to establish microbiological specifications with a "1 0-gram" sample size may not be appropriate for all API's used in nasal spray products. Specifically, some of the peptide and protein products are extremely expensive and the amount of API required for batch manufacture may be in the 1 O-gram range. In these cases the amount of API in the formulation is so small that it has a negligible impact on the overall microbial quality of the product. We recommend that peptide and protein products, and API's which do not contain significant amounts of water be except from this requirement.

Line 176 Surface area is another potential requirement for which standardized compendia1 test methods do not exist, and which is intended primarily to apply to materials used in tablets. We recommend deleting surface area.

Line 188 The statement that the Agency laboratories will ". . .validate the adequacy of the methodology" may be misusing the validation term. The manufacturer of the laser instrumentation states that the method can not be validated, but rather the instrument must be periodically calibrated. Therefore, we recommend that the word *"verify"* be substituted in this sentence for the word "valid&e".

Line 192 This entire paragraph covers material already covered in ICH Q3A and subsequent FDA guidelines and is therefore redundant. The following statement should replace it; *"The ICH Q3A guideline on impurities in drug substances should be applied to nasal and inhalation products."*

Line 211 Since nasal sprays are not targeted to the same sensitive population as the inhalation products; it should be clarified that the entire paragraph is addressing inhalation products and not nasal sprays.

Line 222 While we understand the basis for the request for test data on three lots of excipients, we have concerns about the requirement. It would only makes sense to use the same lots of excipients to manufacture the required three batches of drug product used for the in-vitro comparisons. And it is this that causes our concerns.

The manufacturer's lots of some of these materials, e.g. carboxymethylcellulose, are very large. So significant time can pass

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before additional lots may be available. The purchase of enough material to manufacture demonstration batches from three lots may cover significant percentage of the normal development time for a generic product greatly extending the time required. It is not uncommon to use a single lot of one of these materials for more than a year in routine production. The processes for manufacturing these materials results in lots that can vary significantly. Thus subsequent lots may have significantly differing properties. Thus three lots of test product could have significant variability. In comparison, three reference listed product lots could use the same lot of suspending agent thus artificially leading to less variability in their product. Our experience has also been that if we set tighter specifications than the manufacturer for these materials we may be out of supply for significant periods of time. Based on this discussion we look for assistance in making meaningful comparisons on which the Agency acts.

Line 228 The requirement for a DMF for noncompendial excipients is a new and unnecessary regulatory requirement. The requirements for nasal sprays and inhalation solutions should be no different than those for any other dosage forms. We recommend rewriting this paragraph to require only adequate controls and methodology.

If the intent was to cover "new" excipients that have not previously been administered by these routes, then the section must be rewritten completely, as many compendia1 excipients have never been used in these dosage forms.

Line 241 Very few excipients are suspended in the nasal spray formulations. Examples are suspending agents like microcrystalline cellulose and sodium carboxymethylcellulose. These ingredients are hydrated during the manufacturing creating a particular end viscosity. Thus testing for particle size distribution, crystal form, amorphous content and foreign particulates in the raw materials is unnecessary, since these characteristics will most likely change during the manufacture of the product, and will not necessarily be dependent on the physical characteristics of the raw material listed in this section.

Section III.D.

Line 279 This entire paragraph is covered in specific guidelines for NDA and ANDA applications and is therefore redundant. The following simple statement in the introduction *"Except where explicitly noted, the normal requirements for NDA or ANDA applications apply",* could replace this (and other similar sections).

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Section III.E.

Line 292 **Please consider the following clarifying rewrite of this sentence. "All inhalation drug *products* (solutions, suspensions, and sprays) should be manufactured as sterile products.. ."**

Line 295 **Change the sentence to read as follows: If micronization is used by the *applicant* for the drug substance and/or excipients, the procedure.. .**

Line 298 **insert the following sentence after the period.** *This information may be supplied via a DMF reference when an outside micronizer is employed.*

Line 313 **The one example of a justification that should be included is that which is required to obtain a deliverable volume. Therefore, we recommend inserting the following between "container" and "should", e.g. to** *achieve a labeled deliverable volume,*

Line 318 **Delivery performance is inappropriate and should be removed as an in-process control, as by definition once the pump or actuator assembly is in place the product is finished and no longer in process.**

Section III.F.

Line 342 **The sampling plans used for release or stability testing are covered in the stability requirements and are an inspection or compliance issue and therefore do not need to be part of the application. They certainly have nothing to do with the period of patient use. Therefore, this sentence should read "... analytical procedures ~~with analytical sampling plans~~ should be provided.. ."**

Line 345 **This sentence is redundant to the reference and should be replaced with the simple statement** *"Analytical method must be validated to current standard?."*

Section III.F.I.

Line 357 **Since the manufacturer of the laser instrumentation states that the method can not be validated, but rather the instrument must be periodically calibrated, we recommend adding** *", where applicable,"* **after the word validated.**

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Section III.F.I .a.

Line 360 **Although clarity is used in the title of this section there is no mention of it in the body of the text. The appearance of a formulation is normally described in the context of color and clarity, and this would seem appropriate to incorporate in the text. The appearance of the pump components within the container would appear to be unnecessary if the compatibility of its components were established in a suitable packaging compatibility study.**

Section III.F.1 .c.

Line 381 **The statement which starts "The acceptance criteria should be tight enough to ensure.. . " is a concern as it seems to be attempting to establish a tighter rubric for nasal spray product assays than for other dosage form, yet it is unclear what that should be. The ICH guideline Q6A on setting specifications should apply to these products and this sentence should be reworded to remove any ambiguity.**

Section III.F.I .d.

Line 389 **This section is unnecessary and should be replaced with the following statement.** *The guidelines, ANDA s: Impurities in Drug Products and/or ICH Q3B apply to these products.*

Section III.F.1 .e.

Line 399 **Not all chelating agents are required to achieve satisfactory antimicrobial preservative effectiveness, therefore we recommend changing this line as follows: "...chelating agents,** *if required for antimicrobial preservative effectiveness,* **or other.. ."**

Section III.F.I .f.

Line 406 **We completely agree with the statement in this paragraph-that the pump manufacturer is the primary controller of pump quality. It is common for a single lot of pumps to be used to manufacture multiple lots of product, so we feel the best way to control this parameter is testing of the incoming pump. Thus defective pumps will not be used to manufacture product. This particularly true for solution products where the viscosity is unlikely to vary significantly. So we suggest adding the following to the**

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paragraph. *"For pumps in tended for use in nasal spray product such criteria should be applied* **to** *all receipts of pumps from the manufacturer using appropriate AQL levels. "*

The spray content uniformity test would cover the same issue and it is part of the normal batch release testing.

Section III.F.I .g.

Line 415 **Spray Content Uniformity is a new, unnecessary and confusing term. Uniformity of Dosage Units USP** <905> **commonly referred to as Content Uniformity adequately describes this test. These terms are already applied to Metered Dose Inhalers and would seem to describe the context of this test. We also recommend that the test be submitted to the USP for inclusion as a standardized requirement.**

Line 417 **For nasal sprays that are solutions it should be possible to establish that the amount of active delivered through the nasal pump is directly related to the spray weight. This would be done through two studies, one (the packaging compatibility study) would be a compatibility study with the pump components and the formulation, which would demonstrate that nothing is extracted from the plastic and no active is lost to the plastic. The second study would be a one time demonstration that spray content uniformity, as described in this section, yields the same results whether performed through and assay of each spray or the use of spray weight. With this in mind we recommend the following be added at the end of this section.**

When supported by two appropriate one time studies, the first comparing the Spray Content Uniformity (SCU), **as** *determined via the assay of a single dose delivered through the pump versus the spray weight per actuation,* **and** *the second the. demonstra tion of the lack of loss of active to the pump components in a suitable compatibility study, routine testing of SCU for nasal sprays that are solutions may be determined by spray weight.*

Line 421 The next two sentences misuses the term dose in attempt to define a test method. A minimum dose is the minimum number of sprays actuated into the patient at a single time.. If the label says to actuate one spray into each nostril the dose is two sprays. Therefore, we suggest that the term be used correctly, as that is what is relevant to the patient and the second sentence should be reworded as follows:

"A single dose represents the minimum number of sprays ~~per nostril~~

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specified in the labeling." Or if the intent is to have the test based on the minimum number of sprays rather than the patient dose, then the following wording should replace both sentences. "The number of sprays per determination should not exceed the minimum number of sprays per nostril specified in the labeling."

Line 425 The requirement that the procedure should have controls for actuation parameters effectively mandates the use of automated actuators. We do not believe that the apparatus for performing this test has been adequately standardized for these parameters to be meaningful and recommend against their inclusion at this time. If, however, this is the intention then it should be clearly stated as such.

Line 427 Why express the both the amount of drug delivered and the percent of label claim, since content uniformity type tests always use a percent of label claim rubric? We suggest deleting the requirement to express the result in as the "actual amount."

Line 43 1 The primary purpose of the Spray Content Uniformity is to ensure among multiple containers within a batch. The Spray Content Uniformity through Container Life is the test to ensure uniformity with a container. We recommend rewording this sentence accordingly.

Line 435 It is unnecessary and inappropriate for the Spray Content Uniformity rubric to be tighter for nasal sprays than it is for metered dose inhalers. The devices are used in different patient populations for treating similar diseases. While they represent different technologies, with different limitations, the patients using nasal sprays are not nearly as ill as those using MDIs. Since standard test methods have not been adopted in the industry, limits the same as are used for a potentially more vulnerable population would seem appropriate. Therefore, we recommend replacing the next two paragraphs with the same criteria as USP <905> for pressurized metered-dose inhalers as follows.

Prime and collect a single dose, per label instructions, from 10 containers and analyze. The requirements are met if the amount of active ingredient discharged in not more than 1 of 10 dosage units lies outside the range of 75.0% to 125.0% of the label claim, and no unit is outside the range of 65.0% to 135.0% of the label claim. If 2 or 3 dosage units are outside the range of 75.0% to 125.0% of label claim, prime and collect a single dose, per label instructions, from 20 additional units and analyze. The requirement are met in not more than 3 units of the 30 are

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outside the range of 75.0% to 125.0% of label claim and no unit is outside the range of 65.0% to 135.0% of label claim.

Section III.F. 1. h.

Line 449 **As with SCU we feel that Spray Content Uniformity through life is a new, unnecessary and confusing term. Uniformity of Dosage Units through life (USP <905> commonly referred to as Unit Spray Content) adequately describes this test.**

Line 458 **The reasoning that was used for line 435 above would apply here as well. We recommend the following be substituted for the next two paragraphs.**

Prime and collect **a** *single dose, per* **label** *instructions, from 5 containers and a single dose at the label claim number of sprays per container from each container. Analyze the samples. The requirements are met if the amount of active ingredient discharged in not more than 1 of sprays lies outside the range of 75.0% to 125.0% of the* **label** *claim,* **and** *no spray is outside the range of 65.0% to 135.0% of the label claim. If 2 or 3 sprays are outside the range of 75.0% to 125.0% of label claim, prime and collect a single spray, per label instructions, from 20 additional units containers and* **a** *sing/e spray at the label claim number of sprays per container from each container. Analyze the samples. The requirement are met in not more than 3 sprays of the 30 are outside the range of 75.0% to 125.0% of label claim* **and** *spray is outside the range of 65.0% to 135.0% of label claim.*

Line 453 **In addition, we believe that this type of study is a one time study appropriate only during development and should not be a routine quality control procedure. Once the pump has been demonstrated to be physically stable in a real time stability it is not necessary to demonstrate it for every batch. Therefore we recommend adding the following wording between the sentences on line** 453. *The ability of the pump to meet this requirement over the shelf life of the product needs to be established only during development.*

Section III.F.l .i.

Line 482 **We completely agree with the statement made earlier in the guidance that the pump manufacturer is the primary controller of pump quality. It is common for a single lot of pumps to be used to manufacture multiple lots of product, so we feel the best way to control this parameter is**

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testing of the incoming pump. Thus defective pumps will not be used to manufacture product. So we suggest adding the following to the paragraph. *"Such criteria should be applied to ail receipts of pumps from the manufacturer using appropriate AQL levels."*

Line 489 The comments made earlier regarding sampling plans in response to fine 342 would also apply here. The sampling plans used for release or stability testing are covered in the stability requirements and are an. inspection or compliance issue and therefore do not need to be part of the application. Since the Agency will not be sampling directly from the submission batch this information is not required to allow the ". . .duplication by Agency laboratories." Therefore, we recommend deleted the phrase, "...~~, including sampling plans, . . .~~"

Line 495 Shape is an inherently subjective concept and as such does not belong as an acceptance criterion. This requirement is particularly confusing since the assumption of an essentially elliptical shape is inherent in the following requirement to report the ratio of the axes.

Line 498 Since this is not a comparative test method a drug specific test is unnecessary and will add variability to the test results. Any method that gives an accurate, reproducible spray pattern should suffice for the purposes of this test. Therefore, we recommend dropping the phrase "...~~preferably by a procedure specific for the drug substance~~."

Line 499 For routine testing the spray pattern at a single distance is sufficient to define the acceptable behavior of the pump. The pump manufacturers routinely use a single distance for this purpose. The acceptability of the pump has been established via the procedure in the BA/BE guidance and the purpose of this test if solely to assure that nothing has changed. This is similar in concept to using a dissolution profile to support a BE study but doing single point dissolution for routine batch release. Therefore, we recommend the following rewording of this sentence. "... substance ~~at different distances (e.g. two)~~ *at* a *defined distance* from the nosepiece.. ."

Section III.F.I .j.

Line 507 For nasal sprays the most important aspect of the spray droplet size is that the droplets are sufficiently large to prevent significant inhalation into the lungs. Therefore, for routine testing of droplet size distribution a single cut-off value, with a one sided specification, such as "$\geq$ 90% of the spray $\geq$ 9 microns" based on the performance of the pumps used in

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the clinical or bioequivalence study is sufficient to define the acceptable behavior of the pump.

Line 509 The term "dynamic plume droplet size" has not been defined and we believe that this is the only time it is used. We suggest either the term be dropped from the guidance or defined within it.

The requirement for validation is inappropriate and should be removed. from this sentence.. The manufacturer of the laser instrumentation states that the method can not be validated, but rather the instrument must be periodically calibrated.

We request that a standardized method, such as the USP single stage impactor, be considered satisfactory for routine use in droplet size determinations.

Section III.F.1. k.

Line *519* The validation of this procedure and the sensitivity required to detect shifts, while desirable, is an impractical requirement and should be deleted. In most cases, the particles of suspending agent are present in much higher concentration and are normally of a different particle size distribution. Typically there is 9 or 10 times more suspending agent than there is drug substance. The laser can not be validated as explained above. Even the draft Nasal Spray BE guidance recognizes that there is an ". . .inability to adequately characterize drug PSD.. ." Therefore, we recommend deleting this section entirely.

Section III.F.I .l.

Line529 Microscopic evaluation requires expertise not routinely available in most chemical laboratories and is inherently subjective. Microbiologists are not trained for the types of work being requested. Therefore, we recommend inserting the following rewording of this sentence. "... distribution testing (section III.F.I .k) ~~for both release and stability purposes~~. *During development the submission* batches *should be examined microscopically* at *release and periodically during stability to establish that under the* labeled *storage conditions there* are *unlikely to be any significant changes in* the *suspended API particles."*

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Section III.F.l .m.

Line 540 **The validation of this procedure, while desirable, is an impractical requirement. The only way to perform this test is through visual inspection, perhaps with the aid of magnification. Therefore, the test is inherently subjective and not validatable. The increase in particulate matter from the container closure system should be addressed as part of the packaging compatibility study and therefore this test should only be a release test requirement.**

Section III.F.l .p.

Line 570 **Weight loss should not be a stability requirement for most nasal sprays. While it may be appropriate for semi-permeable containers, such as LDPE, or for formulations that contain a volatile organic component which is not directly tested for, it is not needed for routine nasal sprays. In the unusual circumstance where there is loss from the container it would be quickly detected by the spray content uniformity through container like test requirement. Therefore, we recommend that this paragraph be reworded as follows.**

"Nasal spray drug products should include acceptance criteria for net content ~~and weight loss of stability~~. *For products stored in semi-permeable containers (such as LDPE) or which contain* **a** *volatile organic component, for which there is not a direct test, the weight loss on stability should be determined.* **Since storage orientation plays a key role in any weight loss, the drug product should be stored in upright and inverted or upright and horizontal positions to assess this characteristic."**

, Section III.F.l .q.

Line 580 **This requirement is impractical for the dosage form manufacturer and more appropriately should be part of the pump manufacturers DMF. Which plasticizers, accelerators, antioxidants and vulcanizing reagents were used in the process is often proprietary information. Pumps may container a dozen components each and everyone may be a different plastic or elastomer making specific tests unrealistic particularly for routine stability studies. A much more effective way of assuring control of these components is to pass this requirement back to the pump assembler and assure that adequate controls exist in the DMF.**

A study to determine if any extractables (leachables) **can be detected is an appropriate part of the development process. This would be part of**

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the packaging compatibility study as outlined in the general comments above.

We cannot understand the meaning of extractables testing that requires vigorous extraction with an aggressive organic solvent when the dosage form employs no organic solvent at all. Water will not extract organically soluble material to any significant level. This requirement is a scientific exercise with no meaning to the patient and should be dropped.

We recommend replacing this entire paragraph with a section entitled Packaging Compatibility Study consistent with the recently issued packaging guideline. This one time study demonstrating the lack of extractables would become a required part of the submission.

Section III.F.**1** .s.

Line 600 **This test is only appropriate for formulations that either contain a** tonicity **agent or make a claim regarding tonicity. Therefore, we recommend the following change in wording.** *"for formulations containing* **a** *agent, such as dextrose or sodium chloride, to control the tonicity, or make a label c/aim regarding tonicity* **the osmolality of the formula should be tested and controlled,** *at release,* **with.** .."

Section III.G.

Line 805 We believe **that the narrative on pump selection is inappropriate in this guidance and should be deleted. Selection of the pump should be based on the needs of the patient and the formulation. Once these are established a suitable pump may be selected.**

Line *811* **This guidance should establish a mechanism to encourage and permit generic manufacturers to bring indexing pumps to the market place to the obvious benefit of the patients. The emphasis through out this guidance would make that impossible even though the statement is made that these pumps are desirable and encouraged.**

Line 822 **This line only applies to NDA products and should state so. Generic manufacturers must match existing products so they cannot select material designed to reduce extractables.**

Line 827 **This paragraph treats container closure systems used for inhalations pump products in a manner identical with those used for nasal sprays.**

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This would seem to be an unnecessary regulatory burden on nasal spray products. This paragraph should be rewritten to define the different requirements for nasal spray pumps and inhalation spray pumps. It should describe the studies required to support a one-time packaging compatibility study as described above for nasal sprays and moved into section IV.

The comparisons of long-term stability samples with extraction studies for nasal sprays may seem like a good idea, but is impractical and unnecessary. The specific methods required are not routine methods; they are extremely sensitive methods, which require an extraordinary level of skill on the part of the chemist. They are designed for organic solvents and plastic components, but routine use would be with aqueous formations. Thus the methods may not even work with the formulations.

Conducting such a study on the formulated product only adds analytical difficulties to the study. A more effective way of obtaining the needed data is through a packaging compatibility study and extractable testing or certification requirements for the pump assembler. In addition, the recent addition of the Impurities in Drug Products guidance would mean that an extractable present at 0.1% would trigger an investigation.

Finally, we must remember that the materials used in these pumps are generally recognized as safe (GRAS), and the vehicle in the overwhelming majority of cases is water. If such studies are necessary due to the presence of organic solvents in some formulations these requirements should be made explicit for that specific case and not made into a general requirement.

Line 848 **Items 2, 3, 7 and 8 in this list should be covered in the pump manufacturer's DMF and may not be available to the applicant. All references to pump components are out of place since the assembled pumps are what is available to the drug product manufacturer. We recommend that the opening line of this list be rewritten as follows; "The following information should be included in the drug application** *or referenced in the pump manufacturers DMF."*

Line 861 **The sampling plans used for release of packaging components are an inspection or compliance issue and therefore do not need to be part of the application.**

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Section III.G.1.

Line 885 **There are no mechanisms to supply assembled pumps and the unassembled components as part of an application. They will get lost or potentially confused with other samples. We recommend that the reviewing chemist specifically request them at the appropriate time, if necessary, so we suggest the following rewording.**

"... products be *available, if requested by the Agency* submitted to facilitate the application review process."

Section III.G.2.

Line 889 **The performance of the control extraction studies with any solvent other than the formulation vehicle is a scientific curiosity without meaning to the manufacturer or the patient. What is meaningful is what, under reasonable circumstances, might appear in the product. Therefore, the appropriate study is the extraction of the pump with the formulation vehicle under specified stress conditions. This will determine if any extractable are ever likely to be present in the actual product. This entire subsection should be removed and replaced with the type of study previously discussed as a packaging compatibility study.**

Line 898 **The sampling plans are an inspection or compliance issue and therefore do not need to be part of the application.**

Line 904 **This requirement should only apply to NDAs, as the generic manufacturer must match the reference product as closely as possible in formulation and pump components. For an ANDA safety is assumed based on the reference listed product. Safety data is not even permitted within an ANDA application. Therefore, we recommend the sentence start "For an NDA extraction.. ."**

Line 917 **The types of materials referred to in this sentence are not water soluble and therefore this sentence should add clarity by referring to product vehicles that include organic solvents. We urge the Agency to address these issues through the pump manufacturers DMF and not to burden the dosage form manufacturer with a huge amount of redundant testing.**

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Section III.G.3.

Line 926 **If a lack of significant extractables is determined in the one time study the routine testing of components for extractables is an unnecessary regulatory burden without benefit to the consumer. This section should**

be **reworded to apply only when significant extractable are found in the packaging compatibility study.**

Pump manufacturers do not maintain discrete batches in the sense that all of the components that make up a pump "batch" may not come from the same lot. Therefore, testing a sample of a pump batch may or may not be representative of that batch.

The only way to adequately accomplish what the agency has in mind is to pass the burden back to the pump manufactures. This would greatly reduce the amount of testing required, since it would only have to be performed once. Similarly with the way glass for injectable products is handled we recommend that sub sections 2 and 3 (lines 889 to 942) be replaced with the following.

"Suppliers of assembled spray *pumps for use in nasal sprays must maintain in their DMF's docomen tat-y evidence regarding the extraction profiles of ail components used in their pumps, the safety of these extractables, and the systems in place to assure the continued compliance with the profiles established. Pump manufactures should provide, at least annually, to the dosage form manufacturer a statement of compliance with this requirement, which may be included in regulatory filings."*

This is consistent with and extends the concepts that the sentence which starts on line 964 embodies. Rather than the applicant testing multiple lots the vendor should test multiple lots and make those results available to the Agency though the DMF and to the applicant during an inspection.

It is conceivable that there may be a need to control inhalation spray products more tightly than nasal sprays due to the differences in patient populations. If this is the case then specific requirements for these products should be employed based on these additional requirements.

Line 932 **For aqueous formulations the only suitable solvent for these studies is water. We recommend the following rewording.** "...using **water. If**

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other solvents are present in the formulation, other suitable solvents..."

Section III.G.4

Line 949 See the previous discussion and remove the reference to individual and total extractables.

Line 952 Actuation force is a method requirement and not a performance attribute so it should be removed from this sentence.

Line 957 The usage of the term "identical" is unclear in this context. To be truly identical would require one lot. Is the intent to be one design? What about dose ranging studies? Please clarify.

Line 966 "Multiple" is undefined in this context. Are we to assume that the standard 3-lot rule applies? If so, it would be useful to be explicit.

Section III.H.

Line 981 This entire section is redundant and should be deleted. The reference to the stability guidance starting on line 1001 is sufficient.

Line 1020 Sections b and c are redundant and should be deleted as in previous comment.

Line 1044 The first two paragraphs of this subsection are also redundant and should be deleted per the previous comment.

Line 1083 The reference for ANDAs should be a separate paragraph as in the preceding subsection. The opportunity should be taken to clarify when these products are "complex dosage forms" and when they are not. This is not clear in the draft stability guidance. Therefore, we recommend that the following be added following the reference. *"Inhalation and nasal spray suspensions are considered complex dosage forms for the purpose of stability. Inhalation solutions and nasal spray solutions* are *not considered complex dosage forms for the purpose of stability. "*

Line 1092 This section is redundant and should be removed since it is adequate covered Section III.C.

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Line 1102 **Why are noncompendial excipients in this list of special requirements? If they are not "critical" to the performance of the formulation they do not belong in this list. We recommend deleting everything after the word characteristics.**

Line 1104 **Subsections g, h and i are redundant as covered in line 981 above. In addition, the requirement for three different batches of drug substance should be limited to suspensions as once the API is in solution it will not impact the performance of the product.**

Section IV.

Line1 167 **Historically OGD has refused to discuss studies required for ANDAs prior to an actually filing. Does this indicate a change in policy? The guidance should indicate the mechanism for obtaining such a discussion.**

Line 1174 **Since the issue of spray content uniformity is addressed specifically there is no reason to repeat that work as part of the priming/repriming study. The sentence starting SCU should be deleted.**

Line 1181 **This entire section applies only to NDA products and that fact should be explicit by starting the first sentence with** *"For NDA products.. ."* **The following sentence should be added as a new paragraph.** *"ANDA products* **must** *conduct priming and repriming studies in the orientation that is on the reference product labeling to demonstrate comparability."*

Line 1200 **The study proposed is excessive in two ways. (1) As outlined the product is exposed to 84 to 112 temperature cycles and would require specialize equipment. This greatly exceeds the number of cycles and extremes of temperature that any product can be expected to be exposed under even the most unusual circumstances and would require investment in equipment not routinely used in the laboratory. (2) Storage of the pumps outside of the manufacturer's recommended- storage condition would inevitably lead to physical distortion and failure in spray weight, or SCU. Thus the interpretation of the data that fails to meet specification becomes impossible.**

In addition, since glass containers will break when frozen, it is recommended that for glass the lower temperature be 2-8°C. Thus a more realistic but meaningful cycle study would be as follows.

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The proposed studies are not consistent with current industry practices or the draft stability guidance. We recommend that the entire section be replaced with the following statement. *"Data from temperature cycling studies, as described in the stability guidance must be submitted* **as** *part of* **an** *application for these products."* **If there is the design to give addition direction for these products we recommend the following.**

"Such a study may consist of ~~three or four 6 hour cycles~~ **a** *cycle every two* ~~per~~ *days excluding weekends,* **between subfreezing temperature** *for plastic containers and refrigeration (2-8°C) for glass containers* **and 40°C for** *three cycles* ~~a period of at least 4 weeks~~**. Periodically through out the study, at the end** ~~of a predetermined number of cycles~~ *of the study* **the samples should be analyzed for appropriate parameters and compared to the control drug product** *If* **an** *out of specification result is obtained for* **a** *pump functionality test, replace the pump and repeat the test. On/y if out of specification results are also obtained with the second pump would the product deemed to be out of specification"*

Line 1206 Add *if applicable* **after the word sterility since it only applies to inhalation products.**

Line 1222 This entire section applies only to NDA products and should state so explicitly.

Line 1264 If the droplet size or particle size changes during the drop-off phase after the labeled number of doses has been delivered what relevance does it have? The patient is getting a dose below that desired, so a change in droplet or particle size can only exacerbate the situation. The data requested here is uninterpretable and essentially meaningless and should not be required.

Line 1274 Since there are no standardized methods, and the BE/BA guidance clearly states that these methods are not validatable, we do not think they belong as routine stability tests or product characterization. We recommend deleting this section.

Line 1278 Plume geometry is not a CMC issue. Its purpose is comparison between products and manufacturers so it is strictly a BA/BE issue. Recommend deleting this section.

Line 1301 Items M., N. and 0 are issues only for NDAs and should clearly state so.

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Section V.

Line 1332 To allow some flexibility necessary to the generic manufacturer in some situations, we recommend that the phrase "...the same as..." be replaced with "...appropriately close to..."

Section V.A.2.:

Line 1365 NDC Number(s) are optional per 201.2 and should be deleted from the guidance label requirement

Section V.A.3.:

Line 1383 This list should include "sterile" if applicable per 201.57(a)(iv)

Line 1395 Net contents is not required to be included in the Description section per 201.57(a); it would therefore be more appropriate to include "the number of sprays per container" in the "How Supplied" section [which is required per 201.57(k)(2) to include the units in which the dosage form is available]

Line 1396 The number of priming sprays needed before using the unit for the first time and in cases where the unit has not been used for more than a specified period of time is not a requirement of 201.57(a); this information should be placed in the "Dosage and Administration" section. Per 201.57(j), the Dosage and Administration section shall include "specific direction on . . . preparation and administration of the dosage form". It is also a more logical location for practitioners to easily locate this info.

Section V.A.4.:

Line 1409 "Color and appearance of the container, closure and pump components should be included " - detailing the color of the pump components unnecessarily limits the ability to use more than one supplier for these components. The patient leaflet includes diagrams that are representative of the container/closure system.

Line 1411 "A statement that the correct amount of medication in each spray cannot be ensured after the labeled number of sprays..." - similar to the point made for line 1396 above, this information is not required in the How Supplied section per 201.57(j), but would be more appropriately located in the "Dosage and Administration" section which physician's and pharmacists review with patients upon dispensing. It is also included in the Patient Insert where patients can review at home.

Line 1429 "NDC number(s) - not required. See comment on line 1365 above.

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Section V.B.2. :

Line 1493 NDC Number(s) are optional per 201.2 and should be deleted from the guidance label requirement

Section V.B.3. :

Line 1507 This section should include "sterile." if applicable per 201.57(a)(iv)

Section V.B.4. :

Line 1525 "statement should be included that the contents of any partially used container should be discarded" - this information is not required in the How Supplied section per 201.57(j), but would be more appropriately located in the "Dosage and Administration" section which physicians and pharmacists review with patients upon dispensing. It is also included in the Patient Insert where patients can review at home.

Line 1537 NDC Number(s) are optional per 201.2 and should be deleted from the guidance label requirement

Respectfully submitted,

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(These comments can be supplied on a disc or via email if desired.)

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